0 St. 2003

(19) World Intellectual Property Organization International Bureau



(43) International Publication Date 23 November 2000 (23.11.2000)

(51) International Patent Classification7:

PCT

(10) International Publication Number WO 00/69456 A3

- 39/095, 39/155, 39/21, 39/35, 39/00
- (21) International Application Number: PCT/US00/13156
- (22) International Filing Date: 12 May 2000 (12.05.2000)
- (25) Filing Language:

English

A61K 39/39,

(26) Publication Language:

English

(30) Priority Data:

60/133,963

13 May 1999 (13.05.1999) US

- (71) Applicant (for all designated States except US): AMERICAN CYANAMID COMPANY [US/US]; Five Giralda Farms, Madison, NJ 07940 (US).
- (72) Inventor; and
- (75) Inventor/Applicant (for US only): HAGEN, Michael [CA/US]; 12 Summit Oaks, Pittsford, NY 14534 (US).
- (74) Agents: GORDON, Alan, M.; American Home Products Corporation, Patent Law Dept. 2B2, One Campus Drive, Parsippany, NJ 07054 et al. (US).

- (81) Designated States (national): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

- With international search report.
- Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.
- (88) Date of publication of the international search report: 8 February 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



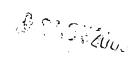
/69456 /

(54) Title: ADJUVANT COMBINATION FORMULATIONS

(57) Abstract: The use of 3-O-deacylated monophosphoryl lipid A or monophosphoryl lipid A and derivatives and analogs thereof, in combination with a cytokine or lymphokine such as granulocyte macrophage colony stimulating factor or interleukin-12 is useful as an adjuvant combination in an antigenic composition to enhance the immune response in a vertebrate host to a selected antigen.

ENT COOPERATION TREAT

PCT

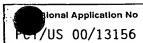


INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

	(
Applicant's or agent's file reference	(Fo	Notification of Transm rm PCT/ISA/220) as w	mittal of Internativell as, where a	tional Search Report pplicable, item 5 below.
33482-00/PCT	ACTION			
International application No.	International filing date (day/m	onth/year) (Earli	iest) Priority Da	te (day/month/year)
PCT/US 00/13156	.12/05/2000		13/0	05/1999
Applicant		· ·		,
,				!
AMERICAN CYANAMID COMPANY		•		
This International Search Report has been according to Article 18. A copy is being tra			nd is transmitted	d to the applicant
This International Search Board consists	of a total of 5	sheets,		
This International Search Report consists It is also accompanied by	a copy of each prior art docume			
it is also accompanied by	a copy of each prior art docume	in oneo in una report.		
Basis of the report				
a. With regard to the language, the	international search was carried	out on the basis of the	e international a	application in the
language in which it was filed, unl	less otherwise indicated under th	is item.		******
the international search w Authority (Rule 23.1(b)).	vas carried out on the basis of a	translation of the inter	national applica	ation furnished to this
b. With regard to any nucleotide an	id/or amino acid sequence disc	closed in the internation	onal application	, the international search
was carried out on the basis of the				,
X contained in the internation	onal application in written form.			•
X filed together with the inte	ernational application in compute	r readable form.		
furnished subsequently to	this Authority in written form.			•
furnished subsequently to	this Authority in computer read	ble form.		
the statement that the sul	bsequently furnished written seq as filed has been furnished.		t go beyond the	disclosure in the
the statement that the infe	ormation recorded in computer r	eadable form is identic	cal to the writter	n sequence listing has been
furnished				
2. X Certain claims were fou	ınd unsearchable (See Box I).			
	·			
3. Unity of invention is lac	oning (ace DUX II).			
A Mish roger to the sist				
4. With regard to the title,	should be a second	•		
the text is approved as si				
the text has been established	shed by this Authority to read as	follows:	•	
1				
				•
5. With regard to the abstract,				
X the text is approved as s	ubmitted by the applicant.			
	shed, according to Rule 38.2(b), the date of mailing of this internation			
6. The figure of the drawings to be pub	olished with the abstract is Figure	No.		
as suggested by the app			[X]	None of the figures.
because the applicant fai			ت	
	-			
Decause this ligure bette	r characterizes the invention.			

INTERMATIONAL SEARCH REPORT



A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K39/39 A61K39/095 A61K39/155 A61K39/21 A61K39/35 A61K39/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07K

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

STRAND, BIOSIS, MEDLINE, CANCERLIT, AIDSLINE, CHEM ABS Data, EMBASE, SCISEARCH, EPO-Internal

Category °	Citation of document, with indication, where appropriate, of t	he relevant passages	Relevant to claim No.	
X -	WO 98 57659 A (SMITHKLINE BEEC ;BOON THIERRY (BE); SILLA SILV 23 December 1998 (1998-12-23)	CHAM BIOLOG /IA (BE); U)	1,2,4,7, 9,11-15, 18,19, 22,25, 27,40, 41,44, 47,49, 51-53, 55,58, 60,62, 63,66, 67,76, 77,79,	
Y	the whole document	-/	80,82-87 3,5,6,8, 10,16, 20,21, 23,24, 26,28,	
χ Furi	ther documents are listed in the continuation of box C.	X Patent family members are listed	in annex.	
"A" docum consi "E" earlier filing the docum which citatic "O" docum other	ent defining the general state of the art which is not dered to be of particular relevance document but published on or after the international date ent which may throw doubts on priority claim(s) or is cited to establish the publication date of another or or other special reason (as specified) ent referring to an oral disclosure, use, exhibition or means ent published prior to the international filing date but than the priority date claimed	 "T" later document published after the Inte or priority date and not in conflict with cited to understand the principle or th invention "X" document of particular relevance; the cannot be considered novel or cannot involve an inventive step when the dc "Y" document of particular relevance; the cannot be considered to involve an indocument is combined with one or ments, such combination being obvious the art. "&" document member of the same patent 	the application but every underlying the claimed invention to considered to current is taken alone claimed invention ventive step when the one other such docu-us to a person skilled	
	actual completion of the international search 20 November 2000	Date of mailing of the international se 04/12/2000	arch report 	
Name and	mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Stein, A		

1

INTERMITIONAL SEARCH REPORT

onal Application No PCT/US 00/13156

	PCT/US 00/13156
·	
Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	42,43, 45,46, 48,50, 54,56, 57,59, 61,64, 65,68, 69,78,81
WO 99 12565 A (SMITHKLINE BEECHAM BIOLOG;GARCON NATHALIE (BE); MOMIN PATRICIA MA) 18 March 1999 (1999-03-18) page 4, line 14 - line 23	3,8,10, 16,21, 26,28, 43,48, 50,54, 59,61
page 5, line 27 -page 11, line 2 claims 1-4,8-13,17-21	-
WO 95 29700 A (UNIV DUKE) 9 November 1995 (1995-11-09) cited in the application the whole document	20,64, 65,68,69
WO 98 56415 A (AQUILA BIOPHARM INC ;UAB RESEARCH FOUNDATION (US)) 17 December 1998 (1998-12-17) page 7, line 31 -page 8, line 11 page 10, line 25 -page 11, line 21 claims 1-20	5,6,23, 24,45, 46,56,57
WO 97 28273 A (NORTH AMERICAN VACCINE INC) 7 August 1997 (1997-08-07) the whole document especially page 5 line 29- page 6 line 4	42,78,81
WO 99 02132 A (CHIRON CORP) 21 January 1999 (1999-01-21)	1,3-6, 9-15,18, 21-24, 27-29, 32-35, 38,39, 51, 54-57, 60-63, 66,67, 70,71, 73,74, 82,83,
page 12, line 1 -page 16, line 29 page 29, line 23 -page 31, line 33 page 33, line 30 -page 35, line 10 -/	
	;GARCON NATHALIE (BE); MOMIN PATRICIA MA) 18 March 1999 (1999-03-18) page 4, line 14 - line 23 page 5, line 27 -page 11, line 2 claims 1-4,8-13,17-21 WO 95 29700 A (UNIV DUKE) 9 November 1995 (1995-11-09) cited in the application the whole document WO 98 56415 A (AQUILA BIOPHARM INC ;UAB RESEARCH FOUNDATION (US)) 17 December 1998 (1998-12-17) page 7, line 31 -page 8, line 11 page 10, line 25 -page 11, line 21 claims 1-20 WO 97 28273 A (NORTH AMERICAN VACCINE INC) 7 August 1997 (1997-08-07) the whole document especially page 5 line 29- page 6 line 4 WO 99 02132 A (CHIRON CORP) 21 January 1999 (1999-01-21) page 12, line 1 -page 16, line 29 page 29, line 23 -page 31, line 33

1

INTERMINIONAL SEARCH REPORT

		<u> </u>
	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Α	AHLERS J ET AL: "Cytokine-in-adjuvant steering of the immune response phenotype to HIV-1 vaccine constructs: Granulocyte-macrophage colony-stimulating factor and TNF-alpha synergize with IL-12 to enhance induction of cytotoxic T lymphocytes" JOURNAL OF IMMUNOLOGY, vol. 158, 1997, pages 3947-3958, XP002153338 cited in the application page 2W	1-87
А	WO 98 17799 A (WANG BIN ;UNIV PENNSYLVANIA (US); APOLLON INC (US); BOYER JEAN D () 30 April 1998 (1998-04-30) especially page 36 lines 17-34 the whole document	1-87
Α	US 5 776 468 A (HAUSER PIERRE ET AL) 7 July 1998 (1998-07-07) the whole document	1-15, 18-87
A	US 5 762 943 A (DOLOVICH JERRY ET AL) 9 June 1998 (1998-06-09) the whole document	16
A	WO 91 16819 A (MOLECULAR RX INC) 14 November 1991 (1991-11-14) the whole document, especially page 9 lines 23-30	17
Α	VASLIN BRUNO ET AL: "Induction of humoral and cellular immunity to simian immunodeficiency virus: What are the requirements for protection?" VACCINE, vol. 12, no. 12, 1994, pages 1132-1140, XP002153339 ISSN: 0264-410X the whole document	29-39, 70-75
P,X	WO 99 40937 A (AMERICAN CYANAMID CO) 19 August 1999 (1999-08-19)	1-14, 51-61, 82-87
	the whole document	
Ρ,Χ	WO 99 27944 A (SCHENK DALE B ;ATHENA NEUROSCIENCES INC (US)) 10 June 1999 (1999-06-10) the whole document	1-14,17

INTERNATIONAL SEARCH REPORT

national application No. PCT/US 00/13156

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 11-17 and 62-87 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This International Searching Authority found multiple inventions in this international application, as follows:
As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark on Protest
No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

on patent family members

ional Application No PCT/US 00/13156

	atent document I in search report		Publication date		atent family member(s)	Publication date
WO	9857659	Α	23-12-1998	WO	9857660 A	23-12-1998
***		•••	20 12 1330	EP	1001808 A	24-05-2000
	·			ĔΡ	0977589 A	09-02-2000
WO	9912565	 А	18-03-1999	AU	9623898 A	29-03-1999
				EP	1009430 A	21-06-2000
WO	9529700	Α	09-11-1995	AU	707894 B	22-07-1999
			•	AU	2372695 A	29-11-1995
				CA	2189045 A	09-11-1995
				EP	0762895 A	19-03-1997
•			•	JP	9512561 T	16-12-1997
				US 	5993819 A	30-11-1999
WO	9856415	Α	17-12-1998	EP	0988053 A	29-03-2000
WO	9728273	Α	07-08-1997	AU	2115897 A	22-08-1997
				EP	0877816 A	18-11-1998
				HU	9901039 A	28-07-1999
	•			NO	983474 A	30-09-1998
		 -	·	PL 	328096 A	04-01-1999
WO	9902132	Α	21-01-1999	AU	8298298 A	08-02-1999
_				EP	1006999 A	14-06-2000
WO	9817799	A	30-04-1998	AU	5002297 A	15-05-1998
			٠	BR	9712852 A	16-11-1999
				EP	0958364 A	24-11-1999
US	5776468	· A	07-07-1998	AU.	685443 B	22-01-1998
•				AU	6426494 A	11-10-1994
				BR	9405957 A	12-12-1995
				DE	69405551 D	16-10-1997
				DE	69405551 T	26-03-1998
				EP	0689454 A	03-01-1996
				FI	954514 A	22-09-1995
				GR	3025483 T	27-02-1998
				JP .	8508722 T	17-09-1996
				NO PL	953759 A	22-09-1995 27-12-1995
				SK	310598 A 117395 A	06-11-1996
	•			AP	515 A	09-08-1996
				Aṛ AT	157882 T	15-09-1996
				AU	705739 B	03-06-1999
				AU	7541696 A	13-02-1997
•			•	CA	2157376 A	29-09-1994
				CN	1119829 A	03-04-1996
				CZ	9502467 A	13-03-1996
				DK	689454 T	08-12-1997
	•			WO	9421292 A	29-09-1994
•				EP	0812593 A	17-12-1997
			•	ES	2109685 T	16-01-1998
				HU	72916 A	28-06-1996
	•			IL	109056 A	15-06-1998
		•		NZ.	263538 A	28-10-1996
				SG	48309 A	17-04-1998
						1, 57 1550

INTERNATIONAL SEARCH REPORT

n on patent family members

ional Application No re-/US 00/13156

				1 .	
Patent doc cited in sear		Publication date		Patent family member(s)	Publication date
US 5762	943 A	09-06-1998	AU	3121497 A	05-12-1997
			CA	2252604 A	20-11-1997
			EP	0914114 A	12-05-1999
			WO	9742947 A	20-11-1997
WO 9116	819 A	14-11-1991	AT	153534 T	15-06-1997
			CA	2081482 A	28-10-1991
			DE	69126304 D	03-07-1997
			DE	69126304 T	04-09-1997
	•		EP	0526511 A	10-02-1993
			JP	2980677 B	22-11-1999
			JP	6502387 T	17-03-1994
	-		US	5851996 A	22-12-1998
			US	5753624 A	19-05-1998
WO 9940	937 A	19-08-1999	AU	2596699 A	30-08-1999
WO 9927	'944 A	10-06-1999	BR	9815357 A	24-10-2000
		:	EP	1033996 A	13-09-2000
			NO	20002784 A	31-07-2000
			AU	1706199 A	16-06-1999